REMARKS

Claim 38 has been canceled without prejudice or disclaimer. Claim 22 has been amended so that the language more closely tracks the language in independent claim 41. The amendment is not made for patentability purposes. The specification has been amended in view of changes to the drawing figures. The attached appendix shows the changes to claim 22 and the changes to the specification. Claims 22 to 25, 37, and 39 to 138 are under consideration.

The Examiner set forth certain informal matters. See the Action at pages 2 and 3. First, the Examiner notes that a new claim 42 was added in the Supplemental Amendment (March 1, 2002) and in the Supplemental Amendment (March 5, 2002). In the Supplemental Amendment (March 5, 2002), applicants requested that the Examiner not enter the Supplemental Amendment (March 1, 2002). In any event, the Examiner is correct that claims 41 and 42 as they exist in the Supplemental Amendment (March 5, 2002) are the correct claims for examination.

Second, the Examiner requested that the title be replaced with a title more indicative of the claims. Action at page 2. The title has been amended above.

Third, the Examiner objected to claims 55 and 96 under 37 C.F.R. § 1.75(c) as allegedly "being of improper dependent form for failing to further limit the subject matter of a previous claim." Action at page 2. Applicants respectfully disagree. Claims 55 and 96 depend from claims 54 and 95, respectively. Part (A) of both claims 54 and 95 indicate that (X) is R or P. Claims 55 and 96 indicate that (X) is R. Accordingly, both claims 55 and 96 further limit the claims from which they depend.

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Fourth, the Examiner objects to the drawings. Action at pages 2 to 3. The Examiner contends that Figures 6 and 7 fail to comply with Rule 84(p)(5), because they contain peak numbers that do not appear in the specification. The brief description of the drawings in the specification has been amended to include references to the peak numbers in the drawings.

The Examiner also objected to Figure 4, because it included upside down text. Action at page 3. Applicants have requested that prior Figure 4 be replaced with new Figure 4, which includes the text in the correct orientation. The change is circled in red ink on the enclosed copy of proposed new Figure 4.

The Examiner also objected to Figures 4, 13, and 15, as including multiple panels that were not separately designated with a number followed by a capital letter. Action at page 3. The Examiner also noted that, if a change was made to include figure numbers and capital letters, the specification should be amended to reflect such changes. Applicants have requested that prior Figures 4, 13, and 15 be replaced with new Figures 4, 13, and 15. Those figures now include figure numbers followed by capital letters as requested by the Examiner. Also, the specification has been amended to reflect such changes.

Fifth, the Examiner indicated that the oath or declaration is defective. Action at page 3. Applicants request that the Examiner hold that issue in abeyance until the Examiner indicates allowable subject matter.

The Examiner rejected certain claims under the judicially created doctrine of obviousness-type double patenting in view of U.S. Patent No. 5,075,222. See Action at

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page 4. If the Examiner holds that all of the pending claims are otherwise allowable, applicants will file a terminal disclaimer in view of that patent.

The Examiner rejected claims 38, 41 to 53, 98 to 104, 106, 116-122, 124, 137, and 138 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Action at page 4.

The Examiner stated that claims 38 and 41 are indefinite because she could not discern any difference in their scope. *Id.* Solely to expedite prosecution, claim 38 has been canceled. Thus, that basis for the rejection is moot.

The Examiner rejected claims 98 and 106 because she could not discern any difference in their scope. *Id.* The Examiner also rejected claims 116 and 124 because she could not discern any difference in their scope. *Id.* Applicants respectfully traverse.

Both claims 98 and 116 recite that "said host cell is not capable of glycosylation ***or is a non-human host cell***." Both claims 106 and 124 recite that "said recombinant polypeptide is nonglycosylated." Accordingly, the scope of claims 98 and 106 is different, and the scope of claims 116 and 124 is different.

Applicants respectfully request reconsideration and withdrawal of the § 112, second paragraph, rejection.

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Please grant any extensions of time required to enter this paper and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: November 18, 2002

By: _____

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APPENDIX

IN THE SPECIFICATION:

Paragraph beginning on page 17, line 8:

Figure 4 depicts the mono S ion exchange chromatography of: Figure 4A; Chromatogram A, the pegylation reaction mixture of $mPEG_{5000}^{*}$ IL-1ra, peak 1 is the modified and peak 2 is the unmodified IL-1ra; and Figure 14B; Chromatogram B, shows the purified $mPEG_{5000}^{*}$ IL 1-ra.

Paragraph beginning on page 17, line 16:

Figure 6 depicts the reverse phase HPLC fractionation of tryptic digest of alkylated $mPEG_{5000}$*IL-1ra reacted with tritiated iodoacetic acid to label free cysteines. Separation was performed on a Brownlee C8 (2.1 x 220mm) column at ambient temperature and a flow rate of 1000 µl/min with a linear gradient. Solvent A was 0.1% TFA in water and solvent B was 0.085% TFA in 80% acetonitrile and 20% H_2O. Figure 6 shows peaks 1 through 18.

Paragraph beginning on page 17, line 24:

Figure 7 depicts the reverse phase HPLC fractionation of chymotryptic digest of peptide 18 in figure 6. Conditions were identical to those in figure 6. Peptides 5 and 8 contained tritium counts and peptide 5 had the amino acid sequence LCTAMEADQPVSL. The cysteine was identified as the carboxymethylcysteine derivative. This cycle was the only one containing counts above background. The amino acid sequence of peptide 8 began with serine 103 of IL-1ra. Redigestion of this

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peptide with chymotrypsin permitted fractionation of all tritium counts from the peptide. Figure 7 shows peaks 1 through 7.

Paragraph beginning on page 18, line 17:

Figure 13 compares IL-6 levels induced in mice by five ratios of c105 30kDa TNF inhibitor to TNF (Figure 13A) and five ratios of c105 30kDa TNF inhibitor to PEG_{2000}db to TNF (Figure 13B).

Paragraph beginning on page 18, line 24:

Figure 15 depicts percent neutrophils induced by varying ratios of TNF to c105 30kDa TNF inhibitor (Figure 15A), c105 30kDa TNF inhibitor PEG_{3500}db (Figure 15B); c105 30kDa TNF inhibitor $PEG_{10,000}$db (Figure 13C); and c105 30kDa TNF inhibitor $PEG_{20,000}$db (Figure 15D).

Paragraph beginning on page 42, line 13:

The $mPEG_x$*IL-1ra can be purified using a MonoS (Pharmacia) column with 20mM MES buffer at pH 5.5. The proteins were eluted from the column using a salt gradient from 0 to 500mM NaCl in the same buffer. For example, unmodified IL-1ra elutes at 220mM NaCl, while the purity is assessed by various techniques including analytical ion exchange chromatography and SDS-PAGE. $mPEG_{5000}$ IL-ra elutes at 160mM (Figures 4A and 4B).

Paragraph beginning on page 42, line 32:

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Purified $mPEG_x$*IL-1ra gave a single symmetrical peak upon rechromatography on MonoS and appeared pure by both SDS-PAGE and size exclusion chromatography (Figure 3 and Figure 4B). A comparison of the tryptic maps of IL-1ra and $mPEG_{5000}$*IL-1ra showed one peak, corresponding to the peptide containing c116 and c122, absent from the conjugate map with the appearance of a new broad peak in this map. Subdigestion of this new peak with chymotrypsin and subsequent amino acid sequence analysis indicated that c116 had been pegylated under the conditions employed (Figure 6).

Paragraph beginning on page 54, line 28:

The potency of c105 30kDa TNF inhibitor PEG_{2000} dumbbell with that of the unpegylated c105 30kDa TNF inhibitor was compared. Human recombinant TNF was injected intravenously at a dose of 10ug per mouse either alone or simultaneously with the TNF inhibitors. Four different reactions of inhibitors to TNF were tested (Figures 13A and 13B). The ratios were calculated based on protein content. Three mice were tested at each dose. Blood was collected at two hours after the intravenous injections. IL-6 levels were measure by ELISA.

Paragraph beginning on page 57, line 6:

The potency of unpegylated c105 30kDa TNF inhibitor with three pegylated species of c105 30kDA TNF inhibitor ($PEG_{3,500}$, $PEG_{10,000}$ and $PEG_{20,000}$ dumbbells) was also compared. Keeping the TNF stimulus constant at 7.5 ng per mouse, the inhibitors were tested at ratios of 100:1, 10:1, and 1:1 (c105 30kDa TNF inhibitor species: TNF).

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The ratios were calculated based on protein content. The mice were injected subcutaneously with the c105 30kDa TNF inhibitor simultaneous to the intraperitoneal administration of TNF. Six mice were tested in each dose group. Four hours later the peritoneal lavage fluid was collected and analyzed. Values shown in Figures 15A, 15B, 15C, and 15D are the percentage neutrophils in the peritoneal lavage fluid. The lowest ratio at which the unpegylated c105 30kDa TNF inhibitor and c105 30kDa TNF inhibitor $PEG_{3,500}$ dumbbell significantly inhibited neutrophil migration is 100:1. The c105 30kDa TNF inhibitor $PEG_{10,000}$ and $PEG_{20,000}$ dumbbells significantly inhibited neutrophil migration at a ratio of 10:1.

IN THE CLAIMS:

22. (Twice Amended) An isolated nucleic acid molecule comprising a nucleic acid sequence encoding an interleukin-1 inhibitor (IL-1i) polypeptide, [said polypeptide being capable of inhibiting IL-1,] having interleukin-1 (IL-1) inhibitory activity, wherein said polypeptide is selected from the group consisting of:

A) a polypeptide comprising all or an IL-1 inhibitory fragment of the amino acid sequence:

(U) (X) P S G R K S S K M Q A F R I W D V N Q K T F Y L R N

N Q L V A G Y L Q G P N V N L E E K I D V V P I E P H A

L F L G I H G G K M C L S C V K S G D E T R L Q L E A V

N I T D L S E N R K Q D K R F A F I R S D S G P T T S F

E S A A C P G W F L C T A M E A D Q P V S L T N M P D E

G V M V T K F Y F Q E D E

wherein (U) is M or nothing and (X) is R or P; and

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B) a polypeptide that is at least about 70% homologous to the amino acid sequence set forth in A).

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